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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/846,893	05/01/2001	J. Kevin Judice	P-105-R	5900

21186 7590 03/10/2004

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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/846,893	JUDICE ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12-10-03*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 14-17* is/are pending in the application.

4a) Of the above claim(s) *14-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1-10 and 14-17 are pending.

Applicants' amendment (filed 10 December 2003), which amends claims 1 and 5-6 has been entered. Note that claims 11-13 and 18-19 have been canceled by applicants (see the amendment filed 15 May 2003).

Claims 1-10 are pending to which the followings are or remain applicable. Please note that ground of objection and/or rejection not explicitly restated and/or set forth below are withdrawn.

Election/Restrictions

The applicants' response filed 10 December 2003 asserts that if examination of all inventions in a patent application can be made without serious burden, examiner is required to conduct examination of the entire application even though inventions are independent or patentably distinct, and quotes "see MPEP 803" (see page 13). The applicants' argument is unpersuasive because applicants misinterpret MPEP803, which clearly indicates that there are two criteria for a proper requirement for restriction between patentably distinct inventions: (A) The inventions must be independent (see MPEP § 802.01, § 806.04, § 808.01) or distinct as claimed (see MPEP § 806.05 -§ 806.05(i).

Invention I is related to Invention II as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP

§ 806.05(h)). In the instant case, the component of the pharmaceutical composition, i.e., cyclodextrin can be used to assess a real time interaction between cyclodextrin and cyclodextrin glycosyltransferase on a gold surface in a surface plasma resonance instrument, for example.

Thus, the restriction requirement is still deemed proper and is therefore made FINAL.

The response also discusses the issue regarding rejoinder of process claims upon allowance of product claims (see page 14). Applicants are directed to the following statements with regard to this issue.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined.

See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Applicants are reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Terminal Disclaimer

The terminal disclaimer filed on 10 December 2003 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of Application No. 09/776466 has been reviewed and is accepted. The terminal disclaimer has been recorded.

IDS

It appears that the PTO 1449 form of IDS filed 8 November 2001 is missing. Thus, the references of the IDS will not be listed on any patent resulting from this application because they

were not provided on a separate list in compliance with 37 CFR 1.98(a)(1). In order to have the references printed on such resulting patent, a separate listing, preferably on a PTO-1449 form, must be filed within the set period for reply to this Office Action.

Claim Rejections - 35 USC §102

The rejections under 35 USC 102 (b) stated in the previous Office action are withdrawn in view of the persuasive argument set forth in the response filed 10 December 2003 as the Patel et al. patents do not explicitly teach that the glycopeptide antibiotic is lipidated.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 5 and 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Roberto, D. P. et al. (EP 0463653) taken with Hunt, A. H. et al. (US Pat. No. 4639433), Hirai S.-I. et al. (EP 0094157), Rubinfeld J. (US Pat. No. 6048845) and Pea F. et al. (*J. Antimicrob. Chemother.* (2000) 45, 329-335).

Roberto et al. teach a pharmaceutical composition comprising cyclodextrin, a drug molecule and a pharmaceutical carrier (see the patent claims 1-3), wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin (i.e., 2- hydroxypropyl cyclodextrin) (see the patent claim 6) and the drug molecule is a cyclic peptide antibiotic (see column 5, line 16), as applied to the instant claims 1-2, 5 and 7-8.

Yet, Roberto et al. do not explicitly teach that the said cyclic peptide antibiotic is lipidated glycopeptide (a cyclic glycopeptide) antibiotic.

Hunt et al. teach the lipidated vancomycin derivatives which are cyclic peptide antibiotic and (i) glycosylated (see formula I, column 2), and (ii) lipidated (see abstract, the patent claims 1, 8-13 and Table IV). The said lipidation is made from alkanoic acid modification in which the position R_2 and R_3 form an acyl (i.e., R-CO-) side chain (see column 5, lines 11-15); thus, Hunt's antibiotic is a lipidated glycopeptide antibiotic.

Hunt et al. also teach a pharmaceutical composition comprising the said lipidated glycopeptide antibiotic, e.g., vancomycin derivative (see the patent claims 8-13 and 23-26).

Thus, the Robert's patent *together* with the Hunt's patent are obvious variation over claims 1, 5 and 6 of the current application.

Yet, Roberto et al. and Hunt et al. do no explicitly teach the physical form of the composition and weight percentage of the components that constitute the composition thereof.

Hirai et al. teach a pharmaceutical composition comprising cyclodextrin and an antibiotic (see the patent claims 1-3) and teach that the cyclodextrin content in the composition is preferably about 2-10% by weight (see page 18, lines 11-14), as applied to the instant claims 9-10.

Also, Hirai et al. teach a freeze-dried (i.e., lyophilized) powdery composition (see page 7, line 11), as applied to the instant claims 3-4.

Further, Hirai et al. teach the lipid pharmaceutical composition prepared in water comprising a drug (e.g., antibiotic) and cyclodextrin (see page 8, lines 8-12) wherein the antibiotic is 0.05-40 w/v percent (see page 7, line 25) typically having effective dose 0.05-1 g (see page 18, line 9), and cyclodextrin 2-20 w/w percent (see page 18,lines 11-13). Therefore, water content of the composition would be 40 to 98 weight percent, which meets the limitation set forth in claim 6 of the current application.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the above references because (*a*) Roberto et al. teach a pharmaceutical composition comprising cyclodextrin and peptide antibiotic, (*b*) Hunt et al. teach the type of the peptide antibiotic is a lipidated glyco-peptide antibiotic, and (*c*) Hirai et al. teach a pharmaceutical composition comprising cyclodextrin and the bioactive component, e.g., peptide antibiotic, the weight percent of the cyclodextrin and freeze-dried power form of the composition. When combined, there would be the following advantages: (i) high level of bioavailability (see page 15, line 25), (ii) improved drug efficacy in view of biological half-life of the administrated drug (see page 18, lines 30-34), (iii) low cytotoxicity (see page 18,lines 34-38) and (iv) permutable repeated dose regimens (see page 18, lines 21-38), as taught by Hirai et

al. Cyclodextrin-formulated pharmaceutical composition has an especial benefit for formulating cytotoxic drug, e.g., antibiotic such as glycopeptide antibiotic (e.g., bleomycins) (see abstract, column 5, lines 33-48, column 6, lines 6-48 and column 11, lines 48-53 of the Rubinfeld et al. patent). The benefit taught by Rubinfeld et al. is to reduce/eliminate cytotoxic agent (e.g., cytotoxic antibiotic) caused irritation or ulceration when administering the cytotoxic antibiotic (see column 5, lines 37-43).

Moreover, it has been known in the prior art of record that cyclodextrin formulated in the pharmaceutical composition reduces the cytotoxicity of the composition comprising toxic antibiotic (see the Roberto et al. teaching, especially abstract), which would be noticeably advantageous to the glyco-peptide antibiotics (e.g., vancomycin) which have undesirable nephrotoxicity (see the Pea et al. reference, at page 330, the left column, lines 3-4), and to aminoglycoside antibiotic (e.g., gentamicin) in that cyclodextrin has a protective effect against the antibiotic-induced nephrotoxicity in a mammal (see Uekama, K. et al. (1993) *J. Pharm. Pharmacol.* 45, 745-747).

Given the above motivation, one of ordinary skill in the art would have combined the above reference teachings to develop the pharmaceutical composition comprising the potential toxic glyco-peptide antibiotic and the cyclodextrin for achieving high pharmaceutical efficacy and lower cytotoxicity of the antibiotics. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Applicants' response to the rejection under 35 USC 103(a)

The response filed 10 December 2003 asserts that the rejection provides sufficient motivation to establish a *prima facie* obviousness in this application, but the *prima facie* case can be rebutted by evidence showing that the claimed subject matter possesses a superior or unexpected property (see page 18). To support said unexpected property of the claimed composition, applicants recite the data of Tables 1-2 which show that the claimed composition has "unexpected property, i.e., reducing tissue accumulation of a glycopeptide antibiotic and thereby reducing nephrotoxicity (see pages 18-19). Applicants' argument has been fully considered but it is not persuasive. The ability of cyclodextrin reducing cyto-toxicity of cytotoxic agent, e.g., cytotoxic antibiotics has been taught by Roberto et al. (see abstract and page 5, the left column), and the property of the cyclodextrin protecting against cytotoxic antibiotic-induced nephrotoxicity and reducing antibiotic renal accumulation has been demonstrated by Uekama et al. (see abstract, Figures 2-3 and pages 746-747). Therefore, the property of reducing nephrotoxicity is not new and unexpected, and the applicants' evidence is deemed insufficient to rebut the *prima facie* case of obviousness stated *supra*. Thus, the applicants' argument is not persuasive.

Moreover, the above-stated activity (prosperity) of reducing nephrotoxicity refers to an *intended use* of the claimed composition. There is no patentable weight associated with the use of the said composition comprising cyclodextrin and lipidated glycopeptide antibiotic which structure and biological activity will not be altered due to the use of the composition thereof for reducing nephrotoxicity.

The response discusses the issue regarding use of the Hirai et al. and Rubinfeld pharmaceutical compositions (see pages 20-21). Note that the subject matter of the current

application is directed to the composition rather than a process of using the composition. As stated above, because there is no patentable weight associated with the use of the claimed composition, the applicants' argument is unpersuasive.

Also, the response argues that the Hunt et al. Patent teaches a type of lipidated glycopeptide antibiotic but not a problem of nephrotoxicity of the antibiotic thereof. The applicants' argument is unpersuasive because combination of the Hunt et al. patent with (*i*) the Roberto et al. teach formulation of cyclodextrin with a cyclic peptide antibiotic, and (*ii*) Hunt et al. teach the pharmaceutical composition comprising lipidated glycopeptide antibiotic would have successfully arrived at the current invention (see also the above statement). Note that reducing nephrotoxicity caused by the cytotoxic antibiotic is an inherent property of the composition taught by Hunt et al. and Roberto et al.

Further, the response asserts that the Roberto et al. patent does not teach cyclodextrin ability of reducing cytotoxic effect caused by a cytotoxic compound. The applicants' argument is unpersuasive because Roberto et al. do teach that cyclodextrin reduces the toxic effects caused by compound (see abstract), e.g., cyclic peptide antibiotic (see the bridging paragraph at pages 5-6) which encompasses lipidated glycopeptide antibiotic (see the Hunt et al. patent and the above statement).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL
Samuel Wei Liu, Ph.D.

February 23, 2004

Karen Cochrane Carlson
KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER